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(54) Title: METHOD FOR THE PREPARATION OF CITALOPRAM

(57) Abstract: The present invention relates method for the preparation of citalopram by alkylation of a 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran derivative.

Method for the Preparation of Citalopram

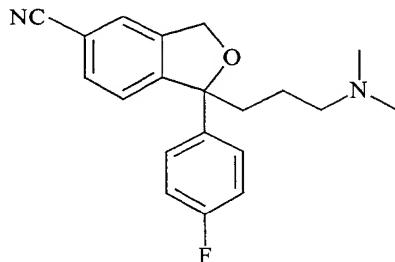
The present invention relates to a method for the preparation of the well-known antidepressant drug citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-

5 isobenzofurancarbonitrile.

Background of the Invention

Citalopram is a well-known antidepressant drug that has now been on the market for some

10 years and has the following structure:



It is a selective, centrally acting serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor,

15 accordingly having antidepressant activities. The antidepressant activity of the compound has been reported in several publications, eg. J. Hyttel *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.* 1982, 6, 277-295 and A. Gravem *Acta Psychiatr. Scand.* 1987, 75, 478-486. The compound has further been disclosed to show effects in the treatment of dementia and cerebrovascular disorders, EP-A-474580.

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Citalopram was first disclosed in DE 2,657,013, corresponding to US 4,136,193. This patent publication describes the preparation of citalopram by one method and outlines a further method, which may be used for preparing citalopram.

25

According to the process described, the corresponding 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile is reacted with 3-(N,N-dimethylamino)propyl-chloride in the presence of methylsulfinylmethide as condensing agent. The starting material was prepared from the corresponding 5-bromo derivative by reaction with cuprous cyanide.

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International patent application No. WO 98/019511 discloses a process for the manufacture of citalopram wherein a (4-(cyano, alkyloxycarbonyl or alkylaminocarbonyl)-2-hydroxymethylphenyl-(4-fluorophenyl)methanol compound is subjected to ring closure. The resulting 5-(alkyloxycarbonyl or alkylaminocarbonyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran is

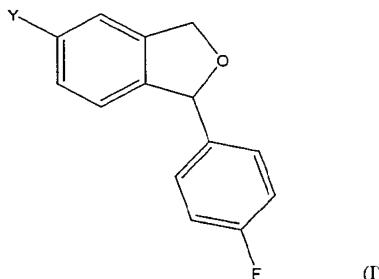
converted to the corresponding 5-cyano derivative and the 5-cyano derivative is then alkylated with a (3-dimethylamino)propylhalogenide in order to obtain citalopram.

It has now, surprisingly, been found that citalopram may be manufactured by a novel 5 favourable process where 5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran is alkylated with a compound which may be converted to a dimethylaminopropyl group.

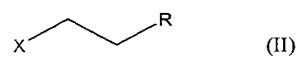
The alkylation process according to the invention is particularly advantageous because the 10 formation of by-products by polymerisation of the alkylating agent is avoided whereby a reduction in the amount of alkylating reagent to be used is made possible. The process of the invention provides high yields.

Summary of the invention

15 Thus, the present invention relates to a method for the preparation of citalopram comprising reaction of a compound of formula (I)



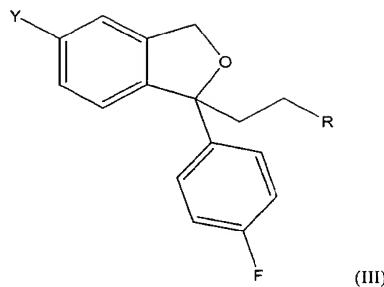
wherein Y is a group which may be converted to cyano, with a compound having the formula



20 wherein X is a suitable leaving group and R is $-\text{CH}_2-\text{O-Pg}$, $-\text{CH}_2-\text{NPg}_1\text{Pg}_2$, $-\text{CH}_2-\text{NMePg}_1$, $-\text{CO-N}(\text{CH}_3)_2$, $-\text{CH}(\text{A}^1\text{R}^1)(\text{A}^2\text{R}^2)$, COOR^3 , $-\text{CH}_2-\text{CO-NH}_2$, $-\text{CH}=\text{CH-R}^7$ or $-\text{CONHR}^8$, wherein Pg is a protection group for an alcohol group, Pg₁ and Pg₂ are protection groups for an amino group, R¹ and R² are independently selected from alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl and aralkyl groups or R¹ and R² together form a chain of 2 to 4 carbon atoms, R³ and R⁷ are independently selected from alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl and aralkyl, R⁸ is hydrogen or methyl and A¹ and A² are selected from O and S;

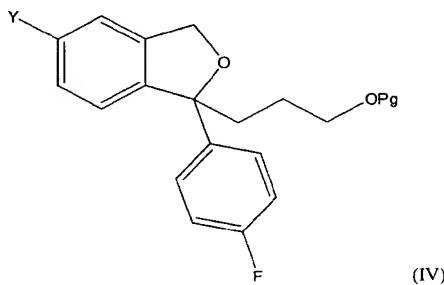
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to form a compound of the formula



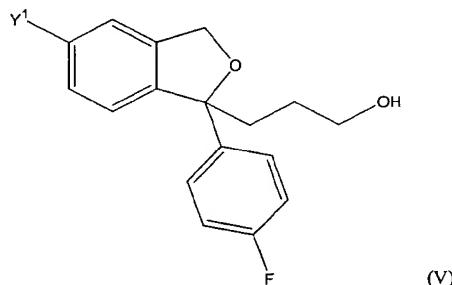
wherein R and Y are as defined above, followed by, in either order, conversion of the group R to a dimethylaminomethyl group and conversion of the group Y to a cyano group, followed
5 by isolation of the citalopram base or a pharmaceutically acceptable acid addition salt thereof.

Thus, in one embodiment, the invention relates to a method for the preparation of citalopram wherein the compound of formula (I) is reacted with a compound of formula (II) wherein R is -CH₂-O-Pg to form a compound of formula



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wherein Y is a group which may be converted to cyano and Pg is a protection group for an alcohol group, optionally followed by conversion of the group Y to a cyano group; and thereafter removal of the protecting group to form a compound of formula



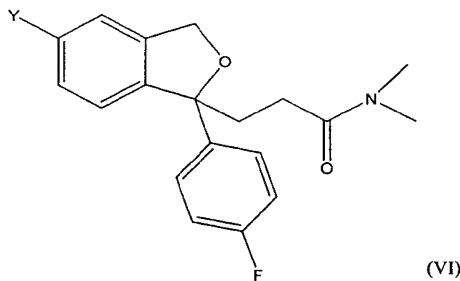
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wherein Y¹ is cyano or a group which may be converted to cyano, and if Y¹ is not cyano, optionally followed by conversion of the group Y¹ to a cyano group; thereafter conversion of

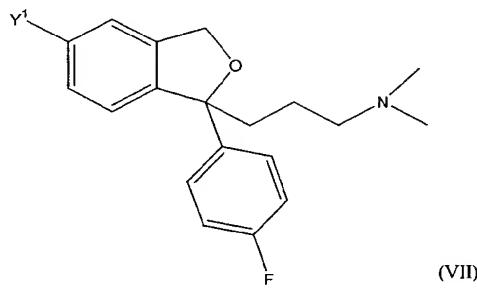
the alcohol group to a feasible leaving group, followed by, in either order, conversion of a group Y^1 which is not cyano to cyano, and replacement of the leaving group with a dimethylamino group by reaction with

5 a) dimethylamine or a salt thereof,
 b) methylamine followed by methylation or reductive amination, or
 c) with an azide followed by reduction to form the corresponding amine and thereafter
 methylation or reductive amination.

10 In a second embodiment, the invention relates to a method for the preparation of citalopram wherein the compound of formula (I) is reacted with a compound of formula (II) wherein R is $-CO-N(CH_3)_2$ to form a compound of the formula

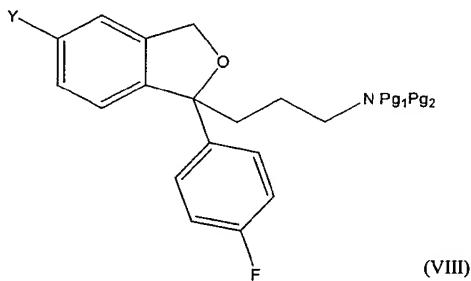


15 wherein Y is as defined above, optionally followed by conversion of the group Y to a cyano group; and thereafter reduction of the resulting compound to form a compound of formula

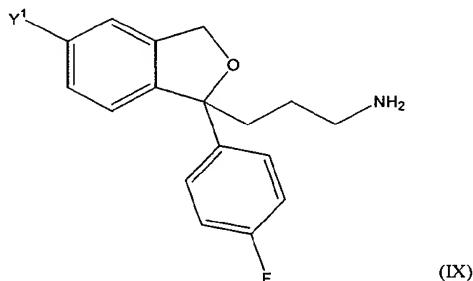


20 wherein Y^1 is cyano or a compound which may be converted to cyano, and if Y^1 is not cyano conversion of the group Y^1 in the compound of formula (VII) to a cyano group.

In a third embodiment, the invention relates to a method for the preparation of citalopram wherein the compound of formula (I) is reacted with a compound of formula (II) wherein R is $-\text{CH}_2\text{-N}(\text{Pg}_1)(\text{Pg}_2)$ to form a compound of formula

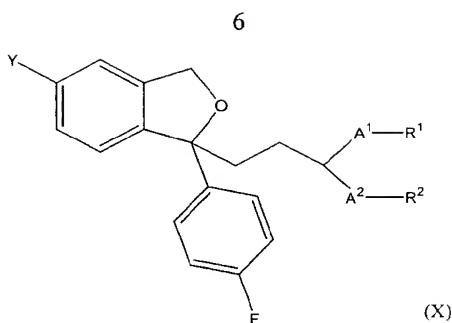


5 wherein Y is a group which may be converted to a cyano group and Pg₁ and Pg₂ are protection groups for an amino group, optionally followed by conversion of the group Y to a cyano group; and thereafter removal of the protecting groups to form a compound having the formula



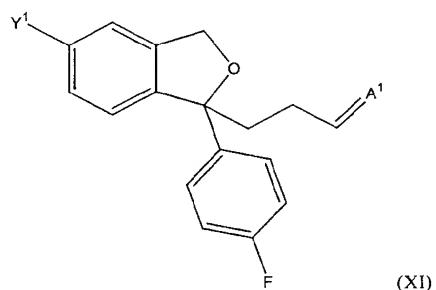
10 wherein Y¹ is a cyano group or a group which may be converted to a cyano group, followed by, in either order, conversion of a group Y¹ which is not cyano to a cyano group and methylation or reductive amination of the free amino group to form citalopram.

15 In a fourth embodiment, the invention relates to a process for the preparation of citalopram wherein a compound of formula (I) is reacted with a compound of formula (II) wherein R is $-\text{CH}(\text{A}^1\text{R}^1)(\text{A}^2\text{R}^2)$ to form a compound of the formula



wherein Y is a group which may be converted to a cyano group, R¹ and R² are independently selected from alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl and aralkyl groups or R¹ and R² together form a chain of 2 to 4 carbon atoms, and A¹ and A² are selected from O and S; optionally followed by conversion of the group Y to a cyano group; and thereafter deprotection of the compound of formula (X) to form a compound of formula

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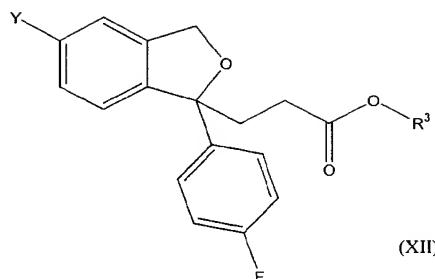


wherein Y¹ is cyano or a group which may be converted to a cyano group and A¹ are as defined above, followed by, in either order, reductive amination with dimethylamine of the compound of formula (XI) and if Y¹ is not cyano, conversion of the group Y¹ to form a

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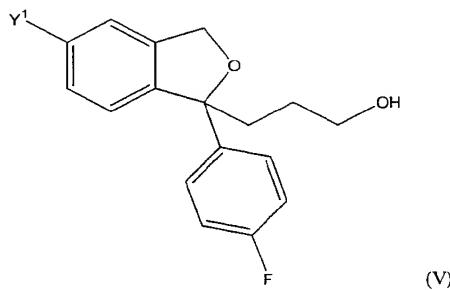
cyano group.

In a fifth embodiment, the invention relates to a method for the preparation of citalopram wherein a compound of formula (I) is reacted with a compound of formula (II) wherein R is -COOR³ to form a compound of the formula



wherein Y is a group which may be converted to cyano and R³ is selected from alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl and aralkyl, optionally followed by conversion of Y to a cyano group; and thereafter

5 i) reduction to form an alcohol of formula



wherein Y¹ is cyano or a group which may be converted to cyano, and if Y¹ is not cyano, optionally followed by conversion of the group Y¹ to a cyano group; and thereafter

10 conversion of the alcohol group to a feasible leaving group, followed by, in either order, conversion of a group Y¹ which is not cyano to cyano, and replacement of the leaving group with a dimethylamino group by reaction with

15 a) dimethylamine or a salt thereof,
 b) methylamine followed by methylation or reductive amination, or
 c) with an azide followed by reduction to form the corresponding amine and thereafter methylation or reductive amination,

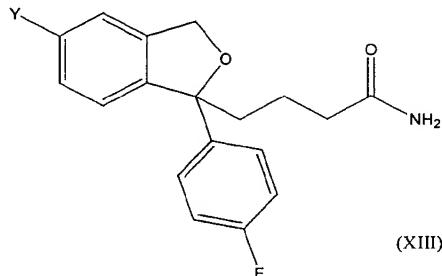
or

20 ii) reaction of a compound of formula (XII) with an amine of formula NH(Me)₂, NH₂Me or NH₃ or a salt thereof to form an amide, followed by, in either order, reduction of the

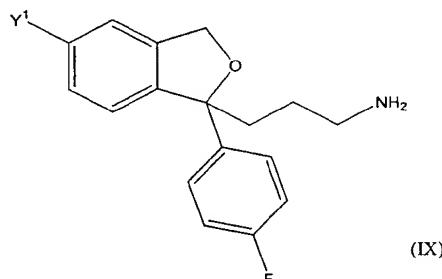
amide, and if Y^1 is not cyano, conversion of the group Y^1 to cyano, and if necessary methylation or reductive amination to form a dimethylamino group.

In a sixth embodiment, the invention relates to a method for the preparation of citalopram wherein a compound of formula (I) is reacted with a compound of formula (II) wherein R is

5 $-\text{CH}_2\text{-CO-NH}_2$ to form a compound of the formula



wherein Y is as defined above, optionally followed by conversion of Y to a cyano group; and thereafter treatment with a hypohalide to form a compound of formula

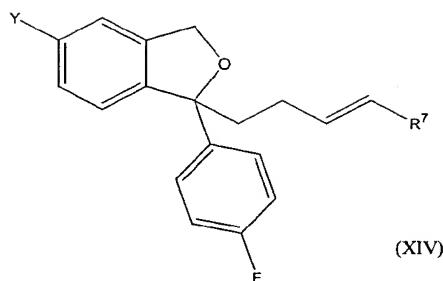


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wherein Y^1 is a cyano group or a group which may be converted to a cyano group, followed by, in either order, conversion of a group Y^1 which is not cyano to a cyano group and methylation or reductive amination of free amino group to form citalopram.

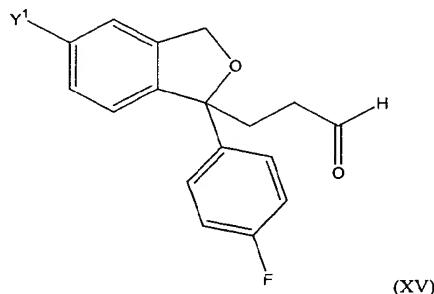
15 In a seventh embodiment, the invention relates to a method for the preparation of citalopram wherein a compound of formula (I) is reacted with a compound of formula (II) wherein R is $-\text{CH}=\text{CH-R}^7$ to form a compound of the formula

9



wherein Y is a group which may be converted to a cyano group and R⁷ is alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl and aralkyl as defined above, optionally followed by conversion of the group Y to a cyano group; and thereafter oxidation to form a compound of formula

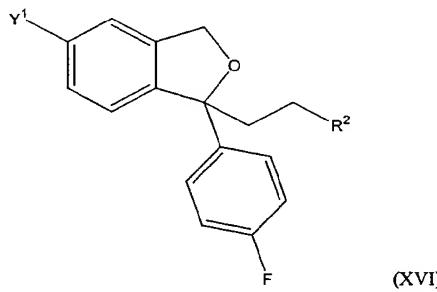
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wherein Y¹ is cyano or a group which may be converted to a cyano group, followed by, in either order, reductive amination with dimethylamine and if Y¹ is not cyano conversion of the group Y¹ to a cyano group to form citalopram.

10

In another embodiment, the invention relates to a method for the preparation of citalopram from a compound of formula



wherein Y¹ is a cyano group, or a group which can be converted to a cyano group and R² is -CH₂-W, wherein W is a leaving group, or R² is cyano or -CH₂N(CH₃)₂ comprising, in either order, conversion of the group Y¹ which is not cyano to a cyano group and conversion of the

15

10

group R² which is not -CH₂N(CH₃)₂ to a dimethylaminomethyl group, followed by isolation of citalopram base or a pharmaceutically acceptable acid addition salt thereof.

According to this method, a group R² which is -CH₂-W, wherein W is a leaving

5 group may be converted to a dimethylaminomethyl group by reaction with

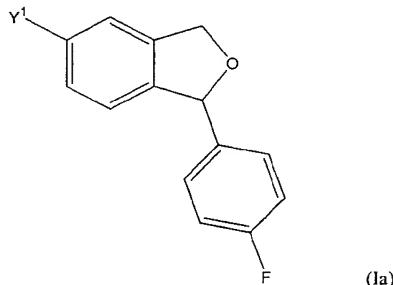
- a) dimethylamine or a salt thereof,
- b) methylamine followed by methylation or reductive amination, or
- c) an azide followed by reduction to form the corresponding amine and thereafter methylation or reductive amination.

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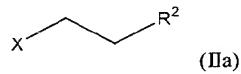
Further, according to this method a group R² which is cyano may be converted to a dimethylaminomethyl group by reduction followed by methylation or reductive amination of the free amino group formed. Reduction of the cyano group to an amino group may be carried out using Rh, Raney Ni etc. as a catalyst.

15

The compound of formula (XVI) may be prepared by reaction of a compound of formula



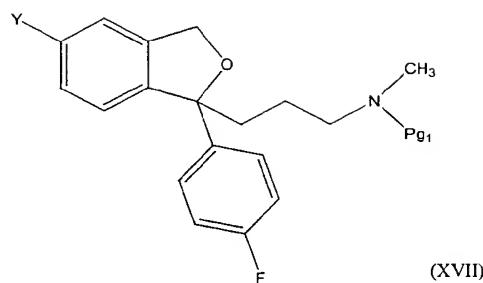
wherein Y¹ is a cyano group, or a group which can be converted to a cyano group, with a compound of formula



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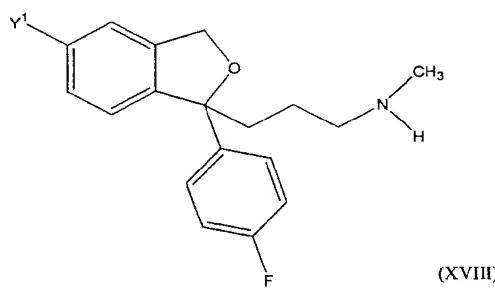
wherein X is a leaving group and R² is -CH₂-W, wherein W is a leaving group, or R² is cyano or -CH₂N(CH₃)₂; provided R² is not -CH₂N(CH₃)₂ when X is halogen and Y¹ is cyano, and if Y¹ is not cyano, optionally followed by conversion of the group Y¹ to a cyano group.

25 In a further embodiment, the invention relates to a method for the preparation of citalopram wherein a compound of formula (I) is reacted with a compound of formula (II) wherein R is -CH₂-NMe(Pg₁) to form a compound of formula



(XVII)

wherein Y is a group which may be converted to a cyano group and Pg₁ is a protection group for an amino group, optionally followed by conversion of the group Y to a cyano group; and thereafter removal of the protection group to form a compound of formula

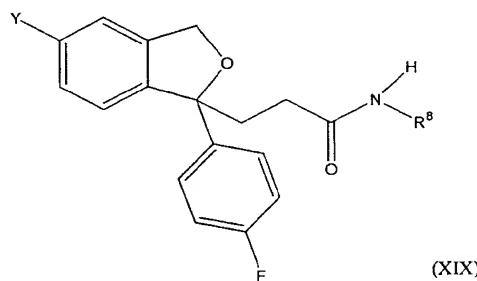


(XVIII)

wherein Y¹ is a cyano group or a group which may be converted to cyano, followed by, in either order, conversion of the group Y¹ which is not cyano to a cyano group and methylation or reductive amination of the amino group to form citalopram.

10

In still another embodiment, the invention relates to a process for the preparation of citalopram wherein a compound of formula (I) is reacted with a compound of formula (II) wherein R is -CO-NHR⁸ to form a compound of formula

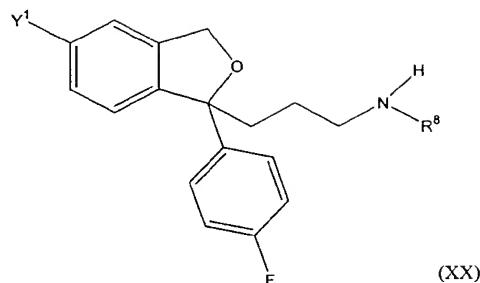


(XIX)

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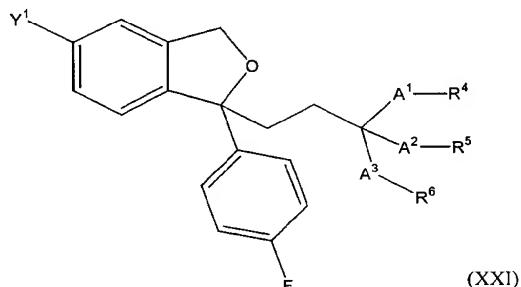
wherein Y is a group which may be converted to cyano and R⁸ is hydrogen or methyl, optionally followed by conversion of the group Y to a cyano group; and thereafter reduction

to form a compound of the formula

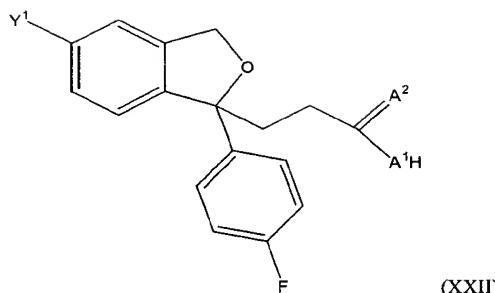


wherein Y¹ is cyano or a group which may be converted to cyano and R⁸ is as hydrogen or 5 methyl followed by, in either order, methylation or reductive amination to form the dimethylamino group and if Y¹ is not cyano, conversion of Y¹ to cyano.

In a further embodiment, the invention relates to a method for the preparation of citalopram comprising reaction of a compound of formula (Ia) with a compound of formula 10 (II) wherein R is $-C(A^1R^4)(A^2R^5)(A^3R^6)$ to form a compound of the formula

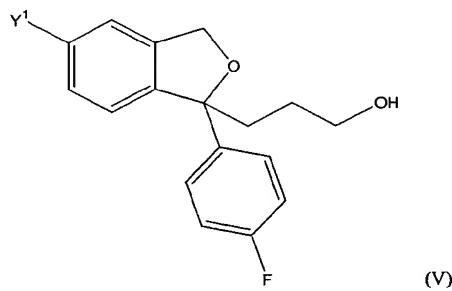


wherein Y¹ is a cyano group or a group which may be converted to cyano and wherein each 15 of R⁴, R⁵ and R⁶ are independently selected from alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl and aralkyl and A¹, A² and A³ is selected from O and S, and if Y¹ is not cyano optionally followed by conversion of Y¹ to a cyano group; and thereafter hydrolysis to form a compound of formula



wherein Y^1 is cyano or a group which may be converted to cyano, and A^1 and A^2 is as defined above and if Y^1 is not cyano, optionally conversion of Y^1 to cyano; and followed by

i) reduction of a compound of formula (XXII) or an ester thereof to form an alcohol of formula



5

wherein Y^1 is cyano or a group which may be converted to cyano, and if Y^1 is not cyano, optionally followed by conversion of the group Y^1 to a cyano group; and thereafter conversion of the alcohol group to a feasible leaving group, followed by, in either order,

10 conversion of a group Y^1 which is not cyano to cyano, and replacement of the leaving group with a dimethylamino group by reaction with

a) dimethylamine or a salt thereof,
 b) methylamine followed by methylation or reductive amination, or
 15 c) with an azide followed by reduction to form the corresponding amine and thereafter methylation or reductive amination,

or

ii) conversion of a compound of formula (XXII) to an amide with an amine of formula
 20 $NH(Me)_2$, NH_2Me , NH_3 or a salt thereof, followed by, in either order, reduction of the amide,

and if Y^1 is not cyano, conversion of the group Y^1 to cyano, and if necessary methylation or reductive amination to form a dimethylamino group.

The invention also relates to the intermediates having the formula (III), (XXI) and (XXII) and 5 intermediates having the formula (V), (VII), (IX), (XVI), (XVIII) and (XI) wherein Y^1 is a group which may be converted to cyano.

In yet another aspect, the present invention relates to an antidepressant pharmaceutical composition comprising citalopram manufactured by the process of the invention.

10

The alkylation step where the compound of formula (I) and (Ia) are reacted with a compound of formula (II) and (IIa), respectively, is suitably carried out by treatment of the compound of formula (I) and (Ia) with a base such as for example LDA (lithiumdiisopropylamine), LiHMDS (hexamethyldisilasan lithium), NaH, NaHMDS (hexamethyldisilasan sodium) and metalalkoxides such as NaOMe, KOMe, LiOMe, NaOtertBu, KOtertBu and LiOtertBu in an aprotic organic solvent such as THF (tetrahydrofuran), DMF (dimethylformamide), NMP (N-methylpyrrolidone), ethers such as diethylether or dioxalane, toluene, benzene, or alkanes and mixtures thereof. The anion formed is then reacted with a compound of formula (II) or (IIa) whereby a group of formula $-CH_2-CH_2-R$ and $-CH_2-CH_2-R^2$ is introduced into position 1 20 of the isobenzofuranyl ring system.

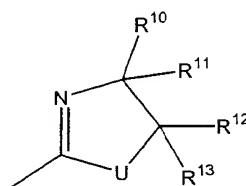
The reaction of the compound of formula (I) and (Ia) and with a compound of formula (II) and (IIa), respectively, is suitably carried out under non-aqueous conditions.

25

Suitable leaving groups X and W, may be a halogenide, or a sulphonate of formula $-O-SO_2-R^0$ wherein R^0 is alkyl, aralkyl, aryl or aryl substituted with alkyl. Conventionally, R^0 is methyl or p-methylphenyl.

30

Groups Y, which can be converted to a cyano group may be selected from halogen, $-O-SO_2-(CF)_n-CF_3$, wherein n is 0-8, -CHO, -COOR', -CONR'R'', -NHR''' wherein R' and R'' are hydrogen, alkyl, alkenyl or alkynyl, or optionally alkyl substituted aryl or aralkyl and R''' is hydrogen or alkylcarbonyl or Y is an an oxazoline or thiazoline group of the formula



wherein U is O or S;

R^{12} - R^{13} are each independently selected from hydrogen and alkyl, or R^{12} and R^{13} together form a C_{2-5} alkylene chain thereby forming a spiro ring; R^{10} is selected from hydrogen and alkyl, R^{11} is selected from hydrogen, alkyl, a carboxy group or a precursor group therefore, or 5 R^{10} and R^{11} together form a C_{2-5} alkylene chain thereby forming a spiro ring.

Y may be any other group, which can be converted to a cyano group.

The substituents R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are preferably alkyl or aralkyl. Suitably, R^1 and R^2 and R^4 , R^5 and R^6 are identical.

10

The alcohol protecting group, Pg, may be a trialkylsilyl group, a benzyl group or a tetrahydropyranyl group (THP).

According to the invention, the alcohol protecting group is removed to form the compound of 15 formula (IV) using conventional methods for removal of the protection group in question.

Thus, where the protecting group is trialkylsilyl the protecting group may be removed by treatment with a base, an organic or mineral acid or a fluoride such as KF, or trialkylaminofluoride.

20

Where Pg is benzyl, the protecting group may be removed by reduction using Pd/C or Pt/C as a catalyst.

Where Pg is a tetrahydropyranyl (THP) group, the protecting group may be removed by 25 treatment with an organic or mineral acid, or resins carrying H^+ groups such as Dowex H^+ or Amberlyst.

The alcohol group in the compound of formula (V) is converted to a feasible leaving group such as halogen, or a sulphonate of formula $-O-SO_2-R^0$ wherein R^0 is as defined above, by 30 reaction with reagents such as thionylchloride, mesylchloride, tosylchloride etc.

The resulting compound is then reacted with dimethylamin or a salt thereof, e.g. M^+ , $N(CH_3)_2$ wherein M^+ is Li^+ or Na^+ . The reaction is suitably carried out in an aprotic organic solvent such as THF (tetrahydrofuran), DMF (dimethylformamide), NMP (N-methyl pyrrolidone), 35 ethers such as diethylether, or dioxane, toluene, benzene, or alkanes and mixtures thereof. The compound of formula (V) carrying a suitable leaving group may also be converted to

citalopram by reaction with dimethylammonium chloride in presence of a base. Alternatively, the compound of formula (V) carrying a suitable leaving group, such as a sulphonate of formula $-O-SO_2-R^0$ wherein R^0 is as defined above, may be reacted with an azide, such as sodium azide, followed by reduction using Pd/C as a catalyst to form a compound of formula 5 (IX) and thereafter methylation or reductive amination to form Citalopram.

The compound of formula (V) carrying a suitable leaving group, may also be converted to citalopram by reaction with methylamine followed by methylation or reductive amination to form a dimethylamino group.

10

In a compound of formula (XVI) wherein R^2 is $-CH_2-W$ wherein W is a suitable leaving group, W may be replaced by a dimethylamino group as described above.

15

The reduction of the amides of formula (VI) and (XIX) is conveniently carried out in toluene using Red-Al as a reducing agent.

Suitable groups Pg_1 and Pg_2 are aralkyl or $-SO_2-R^0$ groups wherein R^0 is as defined above, typically benzyl or tosyl, or Pg_1 and Pg_2 together with the N atom to which they are attached form an optionally substituted phthalimide group.

20

The protecting groups, Pg_1 and Pg_2 , may be removed using conventional methods for removal of such protective groups. The phthalimide groups may thus be converted to an amino group by treatment with hydrazin or methylamine and ethanol.

25

Where the protecting group is an aralkyl group, such as benzyl, it may be removed by reduction, typically in presence of Pd/C or Pt/C as a catalyst.

Protecting groups of formula $-SO_2-R^0$ may be removed by treatment with Red-Al.

30

The amino group in the compounds of formula (IX), (XVIII) and (XX) may be methylated with methylating agents such as MeI and Me_2SO_4 , wherein Me is methyl. The methylation is carried out using conventional procedures for carrying out such reactions.

35

Alternatively, citalopram is formed by reductive amination. According to this procedure, the compound of formula (IX), (XVIII) or (XX) is reacted with compounds such as formaldehyde, paraformaldehyde or trioxan in the presence of a reducing agent such as $NaBH_4$ or $NaBH_3CN$. The reductive amination is carried out using conventional procedures for carrying out such reactions.

The compound of formula (Xa) or (Xb) may suitably be converted to the corresponding aldehyde by treatment with an organic or mineral acid or with or resins carrying H⁺ groups such as Dowex H⁺ or Amberlyst.

5 The resulting aldehyde may be converted to citalopram by reductive amination, i.e. by reaction with dimethylamin in presence of a reducing agent such as NaBH₄ or NaBH₃CN.

The aldehydes of formula (XV) may be converted to a dimethylamino group by analogous methods.

10 The ester derivative of formula (XII) may be converted to citalopram via the corresponding alcohol of formula (V) by reduction of the ester using Red-Al as a reducing agent or via an amide by reaction of the ester with an amine, preferably NH₂(Me)₂ or a salt thereof. The reduction of the amide may suitably be carried out in toluene using Red-Al as reducing agent.

15 Conversion of a free amino group or a monomethylamino group to a dimethylamino group may be carried out as described above.

Suitably, the agent useful for conversion of a compound of formula (XIII) to a compound of formula (IX) is NaOH/Br₂.

20 Oxidation of the compound of formula (XIV) may be carried out by treatment of the compound with ozone in a polar solvent such as alcohol, water, acetic acid or esters thereof. Alternatively, the compound of formula (XIV) may be treated with oxidation agents such as NaIO₄, OsO₄/NaIO₄ and KMnO₄.

25 Hydrolysis of a compound of formula (XXI) to form a compound of formula (XXII) may be carried out using mineral acids or organic acids.

Conversion of the compound of formula (XXII) to an alcohol of formula (V) or an amide may suitably be carried out via the corresponding acid chloride. The acid chloride may be prepared by treatment of the acid with POCl₃, PCl₅ or SOCl₂ neat or in a suitable solvent, such as toluene or toluene comprising a catalytic amount of N,N-dimethylformamide. The ester is obtained by treatment of the acid with an alcohol, in the presence of an acid, preferably a mineral acid or a Lewis acid, such as HCl, H₂SO₄, POCl₃, PCl₅ or SOCl₂. Alternatively, the ester may be obtained from the acid chloride by reaction with an alcohol.

30 The ester or the acid chloride is then converted to an amide of by amidation with ammonia or an alkylamine, preferably t-butyl amine.

The conversion to amide may also be obtained by reaction of the ester with ammonia or an alkylamine under pressure and heating.

5 The processes for the conversion of the corresponding alcohol or amide to the dimethylamino group of citalopram have already been described above.

When Y is halogen or $\text{CF}_3\text{-(CF}_2\text{)}_n\text{-SO}_2\text{-O-}$, wherein n is 0-8, the conversion to a cyano group may be carried out by reaction with a cyanide source, for example KCN, NaCN, CuCN, Zn(CN)₂ or $(\text{R}^{15})_4\text{NCN}$, where $(\text{R}^{15})_4$ indicates four groups, which may be the same or 10 different, and are selected from hydrogen and straight chain or branched alkyl, in the presence of a palladium catalyst and a catalytic amount of Cu^+ or Zn^{2+} , or with Zn(CN)₂ in the presence of a palladium catalyst. The conversion of a compound wherein Y is halogen or $\text{CF}_3\text{-(CF}_2\text{)}_n\text{-SO}_2\text{-O-}$, wherein n is 0-8, by reaction with a cyanide source in the presence of a palladium catalyst, may be carried out as described in WO 0013648.

15

When Y is Cl or Br the conversion to a cyano group may also be carried out by reaction with a cyanide source, for example KCN, NaCN, CuCN, Zn(CN)₂ or $(\text{R}^{15})_4\text{NCN}$, where $(\text{R}^{15})_4$ indicates four groups, which may be the same or different, and are selected from hydrogen and straight chain or branched alkyl, in the presence of a nickel catalyst. The conversion of a 20 compound wherein Y is halogen or $\text{CF}_3\text{-(CF}_2\text{)}_n\text{-SO}_2\text{-O-}$, wherein n is 0-8, by reaction with a cyanide source in the presence of a nickel catalyst may be carried out as described in WO 00/11926.

25 The reactions may be performed in any convenient solvent as described in Sakakibara et. al. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1985-1990. Preferred solvents are acetonitrile, ethylacetate, THF, DMF or NMP.

When Y is an oxazoline or a thiazoline of the formula (VI), the conversion to a cyano may be carried out as described in WO 00/23431.

30

When Y is CHO, the conversion to a cyano group may be carried out by conversion of the formyl group to an oxime or similar group by reaction with a reagent $\text{R}^{16}\text{-V-NH}_2$, wherein R^{16} is hydrogen, alkyl, aryl or heteroaryl and V is O, N or S, followed by dehydration with a common dehydrating agent, for example thionylchloride, acetic anhydride/pyridine, 35 pyridine/HCl or phosphor pentachloride. Preferred reagents, $\text{R}^{16}\text{-V-NH}_2$, are hydroxylamin and compounds wherein R^{16} is alkyl or aryl and V is N or O.

When Y is -COOH, the conversion to a cyano group may be carried out via the corresponding acid chloride or ester and amide.

5 The acid chloride is conveniently obtained by treatment of the acid with POCl_3 , PCl_5 or SOCl_2 neat or in a suitable solvent, such as toluene or toluene comprising a catalytic amount of N,N-dimethylformamide. The ester is obtained by treatment of the acid with an alcohol, in the presence of an acid, preferably a mineral acid or a Lewis acid, such as HCl , H_2SO_4 , POCl_3 , PCl_5 or SOCl_2 . Alternatively, the ester may be obtained from the acid chloride by reaction with an alcohol. The ester or the acid chloride is then converted to an amide of by amidation 10 with ammonia or an alkylamine, preferably t-butyl amine.

The conversion to amide may also be obtained by reaction of the ester with ammonia or an alkylamine under pressure and heating.

15 The amide group is then converted to a cyano group by dehydration. The dehydrating agent may be any suitable dehydrating agent, and the optimal agent may easily be determined by a person skilled in the art. Examples of suitable dehydrating agents are SOCl_2 , POCl_3 and PCl_5 , preferably SOCl_2 .

20 In a particularly preferred embodiment, the carboxylic acid is reacted with an alcohol, preferably ethanol, in the presence of POCl_3 , in order to obtain the corresponding ester, which is then reacted with ammonia thereby giving the corresponding amide, which in turn is reacted with SOCl_2 in toluene comprising a catalytic amount of N,N-dimethylformamide.

25 Alternatively, a compound where Y is -COOH may be reacted with chlorosulfonyl isocyanate in order to form the nitrile, or treated with a dehydrating agent and a sulfonamide as described in WO 0044738.

When Y is -NHR'', where R'' is hydrogen, the conversion into cyano is preferably performed 30 by diazotation and followed by reaction with CN^- . Most preferably NaNO_2 and CuCN and/or NaCN is used. When R'' is alkylcarbonyl, the compound is initially subjected to hydrolysis thereby obtaining the corresponding compound wherein R'' is H, which is then converted as described above. The hydrolysis may be performed either in acidic or basic environment.

Starting materials of formula (I) wherein X is halogen may be prepared as described in GB 35 1526331, compounds of formula (I) wherein X is $-\text{O-SO}_2-(\text{CF}_2)_n-\text{CF}_3$ may be prepared analogously to the compounds described in WO 99/00640, compounds of formula (I) wherein X is an oxazoline or a thiazoline group may be prepared analogous to the compounds

described in WO 0023431, compounds wherein X is formaldehyde may be prepared analogously to the compounds described in as WO 99/30548, compounds wherein X is –COOH, and esters and amides thereof may be prepared analogously to the compounds described in WO 98/19511 and compounds of formula I wherein is –NHR¹¹ may be prepared analogously to the compounds described in WO 98/19512.

The reaction conditions, solvents, etc. used for the reactions described above are conventional conditions for such reactions and may easily be determined by a person skilled in the art.

10 The starting material of formula (Ia) wherein Y¹ is a cyano group may be prepared as described in US patent No. 4,136,193 or as described in WO 98/019511.

The compounds of formula (II) and (IIa) are commercially available or may be prepared from commercially available starting materials using conventional techniques.

15 Citalopram is on the market as an antidepressant drug in the form of the racemate. However, in the near future the active S-enantiomer of citalopram is also going to be introduced to the market.

20 S-citalopram may be prepared by separation of the optically active isomers by chromatography.

Throughout the specification and claims, the term alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2,2-dimethyl-1-ethyl and 2-methyl-1-propyl.

Similarly, alkenyl and alkynyl, respectively, designate such groups having from two to six carbon atoms, including one double bond and triple bond respectively, such as ethenyl, propenyl, butenyl, ethynyl, propynyl, and butynyl.

30 The term aryl refers to a mono- or bicyclic carbocyclic aromatic group, such as phenyl and naphthyl, in particular phenyl.

The term aralkyl refers to aryl-alkyl, wherein aryl and alkyl is as defined above.

35 The term optionally alkyl substituted aryl or aralkyl means aryl and aralkyl as above which are optionally substituted with one or more alkyl groups.

Halogen means chloro, bromo or iodo.

Citalopram may be used as the free base, preferably in crystalline form, or as a pharmaceutically acceptable acid addition salt thereof. As acid addition salts, such salts 5 formed with organic or inorganic acids may be used. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p- aminobenzoic, glutamic, benzene sulfonic and theophylline acetic acids, as well as the 8- 10 halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

The acid addition salts of the compounds may be prepared by methods known in the art. The 15 base is reacted with either the calculated amount of acid in a water miscible solvent, such as acetone or ethanol, with subsequent isolation of the salt by concentration and cooling, or with an excess of the acid in a water immiscible solvent, such as ethylether, ethylacetate or dichloromethane, with the salt separating spontaneously.

The pharmaceutical compositions of the invention may be administered in any suitable way 20 and in any suitable form, for example orally in the form of tablets, capsules, powders or syrups, or parenterally in the form of usual sterile solutions for injection.

The pharmaceutical formulations of the invention may be prepared by conventional methods 25 in the art. For example, tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting maschine. Examples of adjuvants or diluents comprise: Corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive, colourings, aroma, preservatives etc. may be used provided that they are compatible with the active ingredients.

30 Solutions for injections may be prepared by solving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to the desired volume, sterilising the solution and filling it in suitable ampoules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

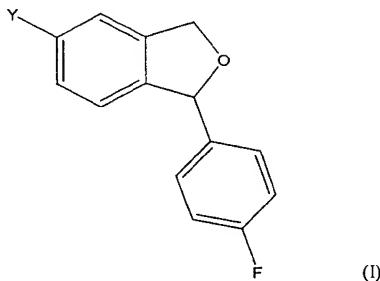
The invention is further illustrated by the following examples.

Example 1

A solution of 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (4.8 g, 0.02 mol) in THF (50 ml) was added dropwise to a solution of LDA (Butyl lithium 1.6 M (15 mL) , 5 disopropylamine 2.6 g) at -30 °C under an atmosphere of nitrogen. After stirring at - 30 °C for 10 minutes, a solution of a compound of formula (II) or (IIa) (0.02 mol) in THF (25 mL) was added dropwise and allowed to warm to room temperature and stirred for a further 60 minutes. The reaction was then quenched with ice, extracted with toluene (3 x 50 mL) , washed with water (50 mL) and concentrated under reduced pressure. The residue was 10 purified by chromatography on silica gel using mixtures of n-heptane/EtOAc as the eluent.

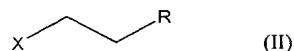
CLAIMS:

1. A method for the preparation of citalopram comprising reaction of a compound of formula (I)



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wherein Y is a group which may be converted to cyano, with a compound having the formula

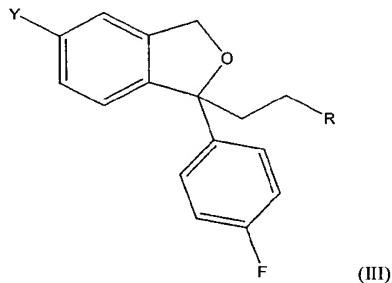


wherein X is a suitable leaving group and R is -CH₂-O-Pg, -CH₂-NPg₁Pg₂, -CH₂-NMePg₁, -CO-N(CH₃)₂, -CH(A¹R¹)(A²R²), -COOR³, -CH₂-CO-NH₂, -CH=CH-R⁷ or -CONHR⁸,

10 wherein Pg is a protection group for an alcohol group, Pg₁ and Pg₂ are protection groups for an amino group, R¹ and R² are independently selected from alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl or aralkyl groups or R¹ and R² together form a chain of 2 to 4 carbon atoms, each of R³ and R⁷ are independently selected from alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl or aralkyl, R⁸ is hydrogen or methyl and A¹ and A² are

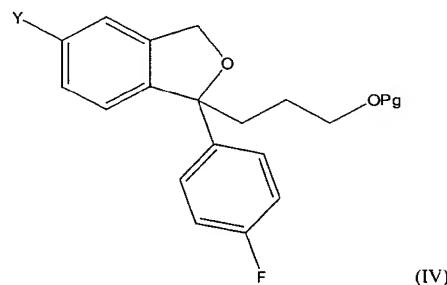
15 selected from O and S;

to form a compound of the formula

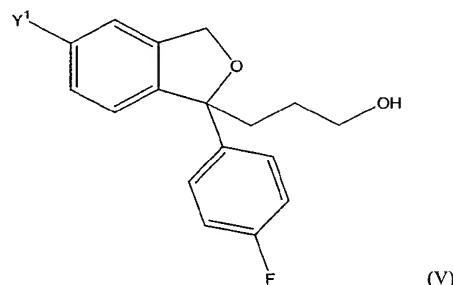


20 wherein R and Y are as defined above, followed by, in either order, conversion of the group R to a dimethylaminomethyl group and conversion of the group Y to a cyano group, followed by isolation of the citalopram base or a pharmaceutically acceptable acid addition salt thereof.

2. The method according to claim 1 wherein the compound of formula (I) is reacted with a compound of formula (II) wherein R is $-\text{CH}_2\text{-O-Pg}$ to form a compound of formula



5 wherein Y is a group which may be converted to cyano and Pg is a protection group for an alcohol group, optionally followed by conversion of the group Y to a cyano group; followed by removal of the protecting group to form a compound of formula



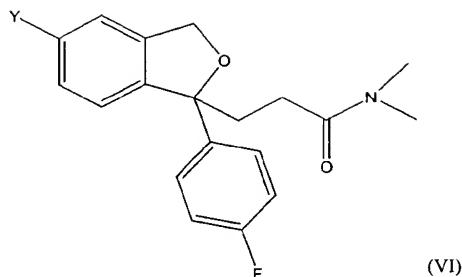
10 wherein Y¹ is cyano or a group which may be converted to cyano, and if Y¹ is not cyano, optionally followed by conversion of the group Y¹ to a cyano group; and thereafter conversion of the alcohol group to a feasible leaving group, followed by, in either order, conversion of a group Y¹ which is not cyano to cyano, and replacement of the leaving group with a dimethylamino group by reaction with

15

- a) dimethylamine or a salt thereof,
- b) methylamine followed by methylation or reductive amination, or
- c) with an azide followed by reduction to form the corresponding amine and thereafter methylation or reductive amination.

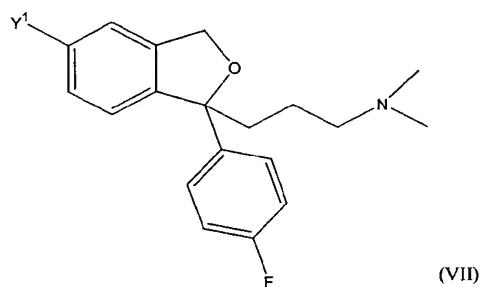
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3. The method according to claim 1 wherein the compound of formula (I) is reacted with a compound of formula (II) wherein R is $-\text{CO-N}(\text{CH}_3)_2$ to form a compound of the formula



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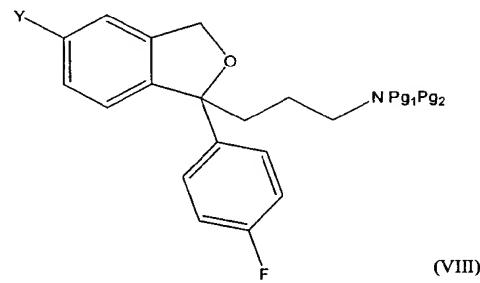
wherein Y is as defined above, optionally followed by conversion of the group Y to a cyano group; and thereafter reduction of the compound formed to form a compound of formula



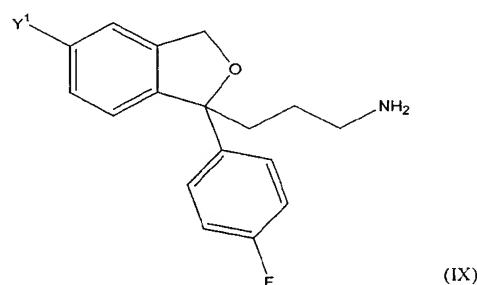
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wherein Y¹ is cyano or a compound which may be converted to cyano, and if Y¹ is not cyano conversion of the group Y¹ in the compound of formula (VII) to a cyano group.

4. The method according to claim 1 wherein the compound of formula (I) is reacted with a compound of formula (II) wherein R is -CH₂-N(Pg₁)(Pg₂) to form a compound of formula



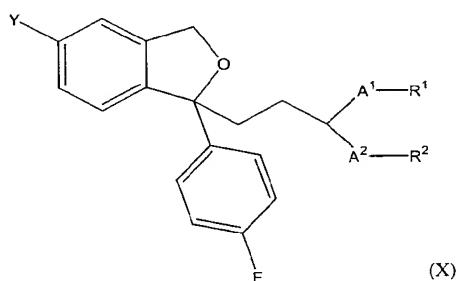
wherein Y is a group which may be converted to a cyano group and Pg₁ and Pg₂ are protection groups for an amino group, optionally followed by conversion of the group Y to a cyano group; and thereafter by removal of the protecting groups to form a compound having the formula



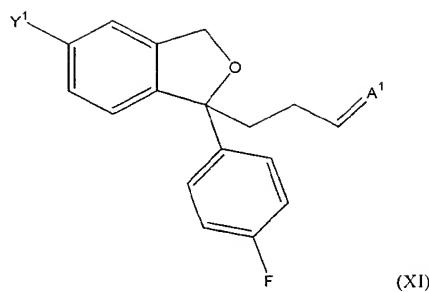
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wherein Y¹ is a cyano group or a group which may be converted to a cyano group, followed by, in either order, conversion of a group Y¹ which is not cyano to a cyano group and methylation or reductive amination of the free amino group to form citalopram.

10 5. The method according to claim 1 wherein a compound of formula (I) is reacted with a compound of formula (II) wherein R is -CH(A¹R¹)(A²R²) to form a compound of the formula

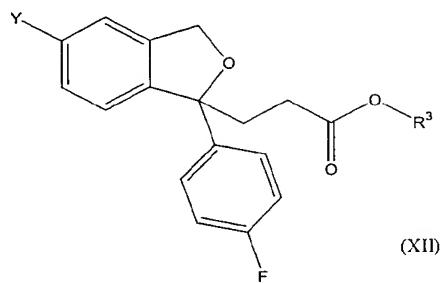


15 wherein Y is a group which may be converted to a cyano group, R¹ and R² are independently selected from alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl and aralkyl groups or R¹ and R² together form a chain of 2 to 4 carbon atoms and A¹ and A² are selected from O and S; optionally followed by conversion of the group Y to a cyano group; and thereafter deprotection of the compound of formula (X) to form a compound of formula



wherein Y^1 is cyano or a group which may be converted to a cyano group and A^1 is as defined above, followed by, in either order, by reductive amination with dimethylamine of the 5 compound of formula (XI) and if Y^1 is not cyano, conversion of the group Y^1 to form a cyano group.

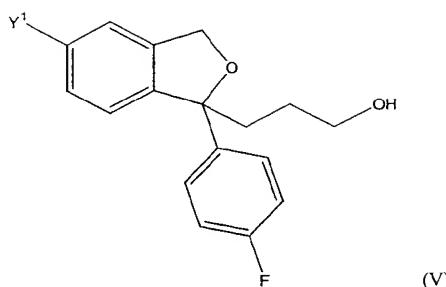
6. The method according to claim 1 wherein a compound of formula (I) is reacted with with a compound of formula (II) wherein R is $-COOR^3$ where R^3 is as defined above to form a compound of the formula



10 wherein Y is a group which may be converted to cyano and R^3 is selected from alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl and aralkyl, optionally followed by conversion of Y to a cyano group; and thereafter

i) reduction to form an alcohol of formula

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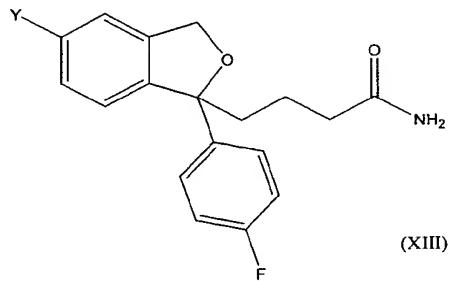
wherein Y^1 is cyano or a group which may be converted to cyano, and if Y^1 is not cyano, 5 optionally followed by conversion of the group Y^1 to a cyano group; and thereafter conversion of the alcohol group to a feasible leaving group, followed by, in either order, conversion of a group Y^1 which is not cyano to cyano, and replacement of the leaving group with a dimethylamino group by reaction with

10 a) dimethylamine or a salt thereof,
 b) methylamine followed by methylation or reductive amination, or
 c) with an azide followed by reduction to form the corresponding amine and thereafter methylation or reductive amination,

or

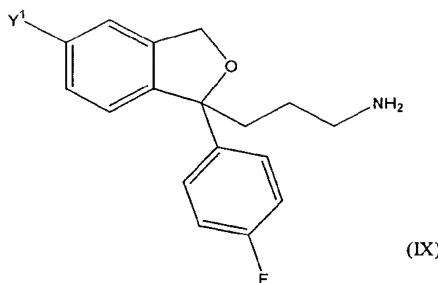
15 ii) reaction of the compound of formula (XII) with an amine of $NH(Me)_2$, NH_2Me , NH_3 or a salt thereof to form an amide, followed by, in either order, reduction of the amide, and if Y^1 is not cyano, conversion of the group Y^1 to cyano, and if necessary methylation or reductive amination to form a dimethylamino group.

7. The method according to claim 1 wherein a compound of formula (I) is reacted with a compound of formula (II) wherein R is $-CH_2-CO-NH_2$ to form a compound of the formula



20

wherein Y is as defined above, optionally followed by conversion of Y to a cyano group; followed by treatment with a hypohalide to form a compound of formula

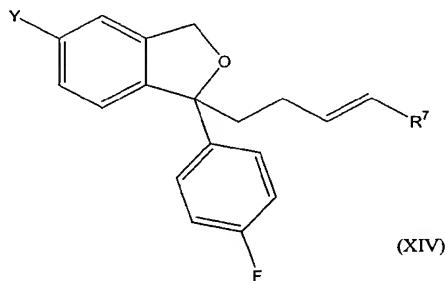


(IX)

wherein Y¹ is a cyano group or a group which may be converted to a cyano group, followed by, in either order, conversion of a group Y¹ which is not cyano to a cyano group and methylation or reductive amination of free amino group to form citalopram.

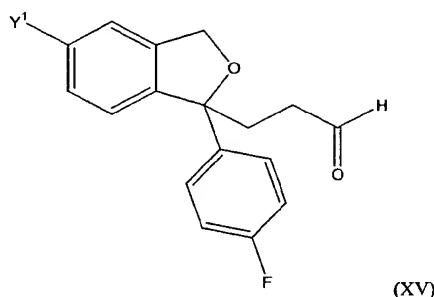
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8. The method according to claim 1 wherein a compound of formula (I) is reacted with a compound of formula (II) wherein R is -CH=CH-R⁷ to form a compound of the formula



(XIV)

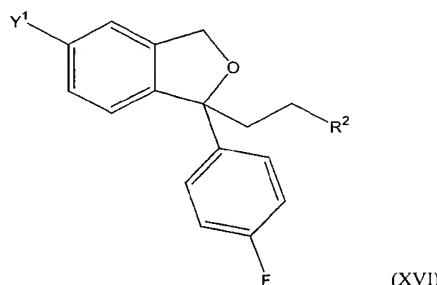
wherein Y is a group which may be converted to a cyano group and R⁷ is alkyl, alkenyl, 10 alkynyl and optionally alkyl substituted aryl and aralkyl as defined above, optionally followed by conversion of the group Y to a cyano group; and thereafter oxidation to form a compound of formula



(XV)

15 wherein Y¹ is cyano or a group which may be converted to a cyano group, followed by, in either order, reductive amination with dimethylamine and if Y¹ is not cyano conversion of the group Y¹ to a cyano group to form citalopram.

9. A method for the preparation of citalopram from a compound of formula

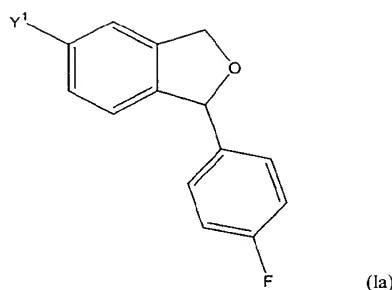


5 wherein Y^1 is a cyano group, or a group which can be converted to a cyano group and R^2 is
 - CH_2 -W, wherein W is a leaving group, or R^2 is cyano or $-CH_2N(CH_3)_2$ comprising, in either
 order, conversion of the group Y^1 which is not cyano to a cyano group and conversion of the
 group R^2 which is not $-CH_2N(CH_3)_2$ to a dimethylaminomethyl group, followed by isolation
 of citalopram base or a pharmaceutically acceptable acid addition salt thereof.

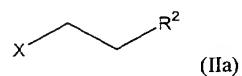
10 10. The method according to claim 9 wherein R^2 is - CH_2 -W, wherein W is a leaving
 group and the group W is replaced by a dimethylaminomethyl group by reaction with
 a) dimethylamine or a salt thereof,
 b) methylamine followed by methylation or reductive amination, or
 c) with an azide followed by reduction to form the corresponding amine and thereafter
 15 methylation or reductive amination.

11. The method according to claim 9 wherein group R^2 is cyano which is converted to a
 dimethylaminomethyl group by reduction followed by methylation or reductive amination of
 the free of the amino group formed.

20 12. The method according to claim 9 wherein the compound of formula (XVI) is prepared
 by reaction of a compound of formula

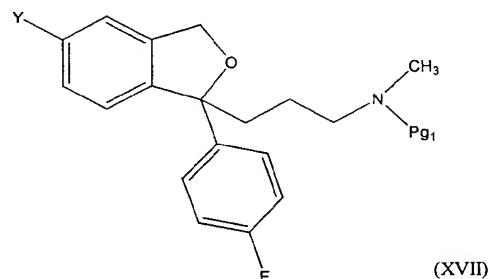


wherein Y^1 is a cyano group, or a group which can be converted to a cyano group, with a compound of formula

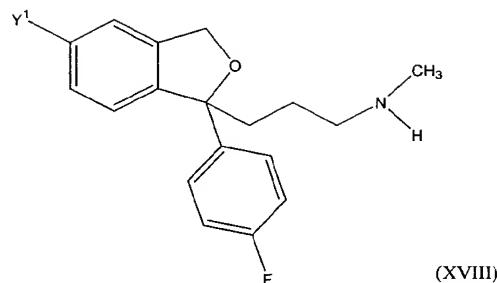


5 wherein X is a leaving group and R² is $-CH_2-W$, wherein W is a leaving group, or R² is cyano or $-CH_2N(CH_3)_2$; provided R² is not $-CH_2N(CH_3)_2$ when X is halogen and Y¹ is cyano; and if Y¹ is not cyano, optionally followed by conversion of the group Y¹ to a cyano group.

10 13. The method according to claim 1 wherein the compound of formula (I) is reacted with a compound of formula (II) wherein R is $-CH_2-NMe(Pg_1)$ to form a compound of formula



15 wherein Y is a group which may be converted to a cyano group and Pg₁ is a protection group for an amino group, optionally followed by conversion of the group Y to a cyano group; thereafter removal of the protection group to form a compound of formula

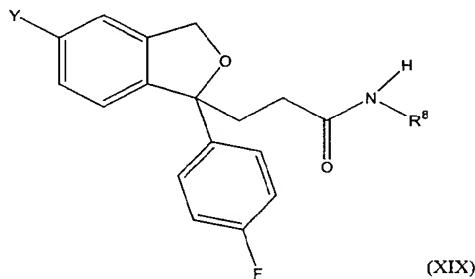


(XVIII)

wherein Y¹ is a cyano group or a group which may be converted to cyano, followed by, in either order, conversion of the group Y¹ which is not cyano to a cyano group and methylation or reductive amination of the amino group to form citalopram.

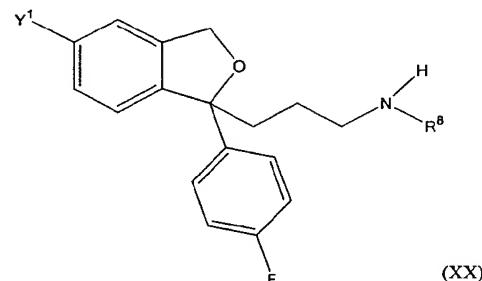
5

14. The method according to claim 1 wherein the compound of formula (I) is reacted with a compound of formula (II) wherein R is -CO-NHR⁸ to form a compound of formula



(XIX)

10 wherein Y is a group which may be converted to cyano and wherein R⁸ is hydrogen or methyl, optionally followed by conversion of the group Y to a cyano group; and thereafter reduction to form a compound of the formula

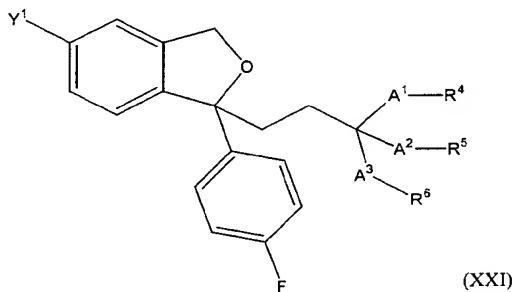


(XX)

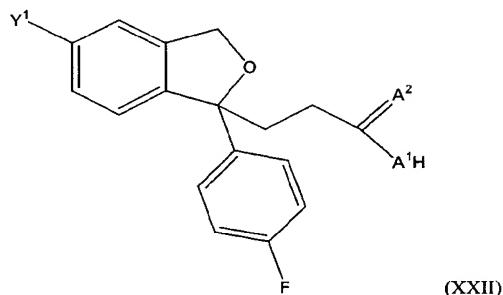
15 wherein Y¹ is cyano or a group which may be converted to cyano and R⁸ is hydrogen or methyl, followed by, in either order, methylation or reductive amination to form a

dimethylamino group, and if Y^1 is not cyano conversion of Y^1 to a cyano group.

15. The method for the preparation of citalopram comprising reaction of a compound of formula (Ia) is reacted with a compound of formula (II) wherein R is $-C(A^1R^4)(A^2R^5)(A^3R^6)$ to form a compound of the formula

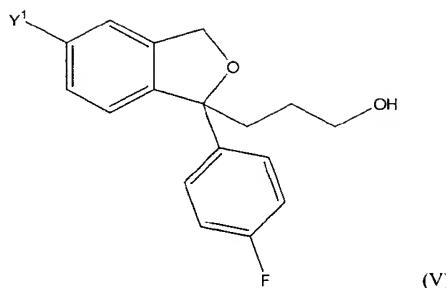


10 wherein Y^1 is a cyano group or a group which may be converted to cyano and wherein each of R^4 , R^5 and R^6 are independently selected from alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl and aralkyl and A^1 , A^2 and A^3 are selected from O and S, if Y^1 is not cyano optionally followed by conversion of Y^1 to a cyano group; and thereafter hydrolysis to form a compound of formula



15 wherein Y^1 is cyano or a group which may be converted to cyano, and A^1 and A^2 are as defined above and if Y^1 is not cyano, optionally followed by conversion of Y^1 to cyano; and followed by

i) reduction of a compound of formula (XXII) or an ester thereof to form a compound of formula



wherein Y¹ is cyano or a group which may be converted to cyano, and if Y¹ is not cyano, optionally followed by conversion of the group Y¹ to a cyano group; and thereafter

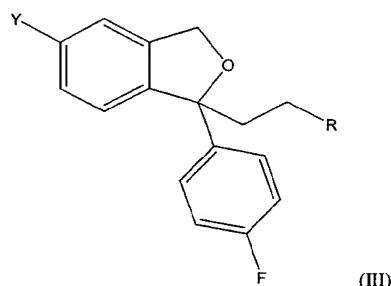
5 conversion of the alcohol group to a feasible leaving group, followed by, in either order, conversion of a group Y¹ which is not cyano to cyano, and replacement of the leaving group with a dimethylamino group by reaction with

10 a) dimethylamine or a salt thereof,
 b) methylamine followed by methylation or reductive amination, or
 c) with an azide followed by reduction to form the corresponding amine and thereafter methylation or reductive amination,

or

15 ii) conversion of the compound of formula (XXII) or an ester thereof to an amide followed by, in either order, reduction of the amide, and if Y¹ is not cyano, conversion of the group Y¹ to cyano, and if necessary methylation or reductive amination to form a dimethylamino group.

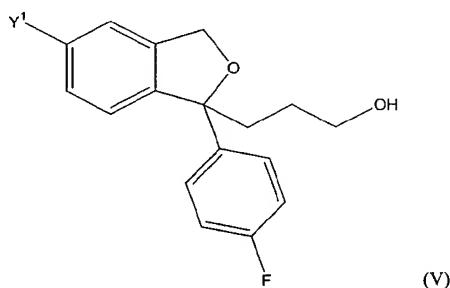
20 16. A compound of the formula



wherein Y is a group which may be converted to cyano and R is -CH₂-O-Pg, -CH₂-NPg₁Pg₂, -CH₂-NMePg₁, -CO-N(CH₃)₂, -CH(A¹R¹)(A²R²), -COOR³, -CH₂-CO-NH₂, -CH=CH-R⁷ or -

CONHR⁸, wherein Pg is a protection group for an alcohol group, Pg₁ and Pg₂ are protection groups for an amino group, R¹ and R² are independently selected from alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl or aralkyl groups or R¹ and R² together form a chain of 2 to 4 carbon atoms, each of R³ and R⁷ are independently selected from alkyl, 5 alkenyl, alkynyl and optionally alkyl substituted aryl or aralkyl, R⁸ is hydrogen or methyl and A¹ and A² are selected from O and S; or an acid addition salt thereof.

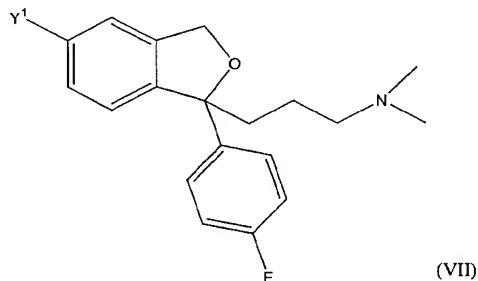
17. A compound of formula



10

wherein Y¹ is a group which may be converted to cyano, or an acid addition salt thereof

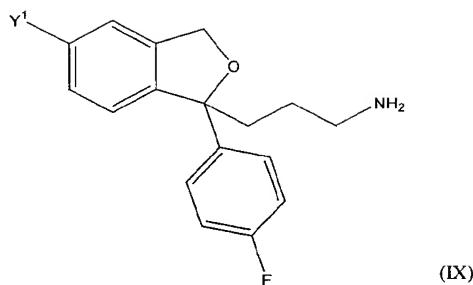
18. A compound of formula



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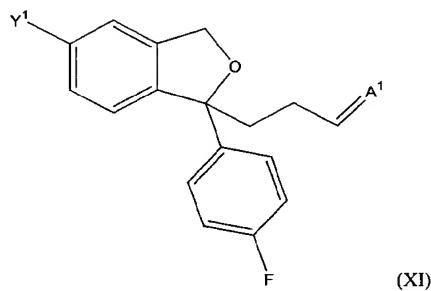
wherein Y¹ is a compound which may be converted to cyano, or an acid addition salt thereof.

19. A compound of formula



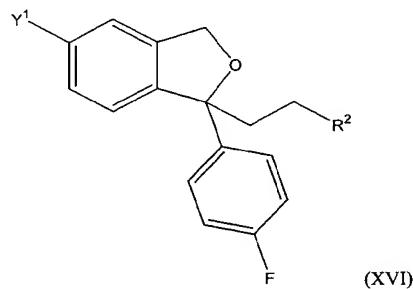
wherein Y^1 is a group which may be converted to a cyano group, or an acid addition salt thereof.

5 20. A compound of formula



wherein Y^1 is a group which may be converted to a cyano group and A^1 is O or S, or an acid addition salt thereof

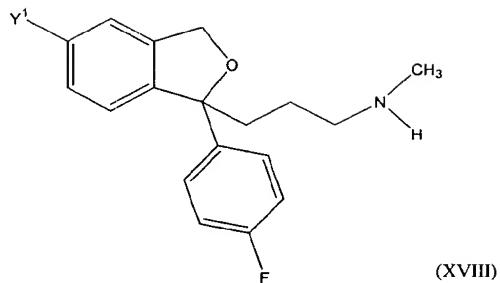
21. A compound of formula



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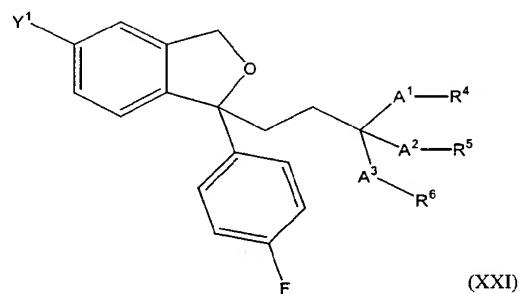
wherein Y^1 is a group which may be converted to a cyano group and R^2 is $-\text{CH}_2\text{W}$, wherein W is a leaving group or R^2 is cyano or $-\text{CH}_2\text{N}(\text{CH}_3)_2$, or an acid addition salt thereof.

15 22. A compound of formula



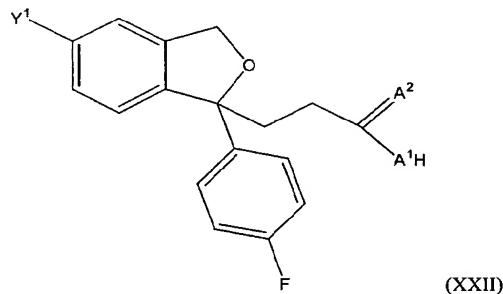
wherein Y^1 is a group which may be converted to cyano, or an acid addition salt thereof.

5 23. A compound of formula



wherein Y^1 is a cyano group or a group which may be converted to cyano and wherein each of R^4 , R^5 and R^6 are independently selected from alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl and aralkyl and A^1 , A^2 and A^3 are selected from O and S, or an acid addition salt thereof.

10 24. A compound of formula



wherein Y^1 is cyano or a group which may be converted to cyano, and A^1 and A^2 is selected from O and S, or an acid addition salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 01/00168

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 307/87

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9819511 A2 (H. LUNDBECK A/S), 14 May 1998 (14.05.98) --	1-24
A	Eur. J. Med. Chem.- Chimica Therapeutica, Volume 12, No 3, 1977, Allan J. Bigler et al, "Quantitative structure-activity relationships in a series of selective 5-HT uptake inhibitors" page 289 - page 295 -- -----	1-24

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

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- "E" earlier application or patent but published on or after the international filing date
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
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Date of the actual completion of the international search

15 June 2001

Date of mailing of the international search report

19 -06- 2001

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INTERNATIONAL SEARCH REPORT

Information on patent family members

28/05/01

International application No.

PCT/DK 01/00168

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9819511 A2	14/05/98	AU 5116798 A	29/05/98
		BG 104487 A	31/01/01
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		DE 1032566 T	15/03/01
		EP 1032566 A	06/09/00
		ES 2149141 T	01/11/00
		NO 20002267 A	06/07/00
		PL 340774 A	26/02/01
		ZA 9810059 A	05/05/99